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Part VI

Department of Health and Human Services

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Recombinant DNA Research, Actions Under Guidelines

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Research; Actions Under Guidelines

AGENCY: National Institutes of Health, PHS, HHS.

ACTION: Notice of Actions under NIH Guidelines for Research Involving Recombinant DNA Molecules.

SUMMARY: This notice sets forth actions taken by the Director, NIH, under the January 1980 NIH Guidelines for Research Involving Recombinant DNA Molecules (45 FR 6724).

EFFECTIVE DATE: November 21, 1981.

FOR FURTHER INFORMATION CONTACT: Additional information can be obtained from Dr. William J. Gartland, Office of Recombinant DNA Activities (ORDA), National Institutes of Health, Bethesda, Maryland 20205. (301) 496–6051.

SUPPLEMENTARY INFORMATION: I am promulgating today several actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules. These were reviewed and recommended for approval by the Recombinant DNA Advisory Committee (RAC) at its meeting on September 25–26, 1980. In accordance with Section IV–E–1–b of the NIH Guidelines, I find that these actions comply with the Guidelines and present no significant risk to health or the environment.

This announcement provides background information on the actions including an analysis of correspondence concerning these actions received up to Octoiber 31, 1980.

Immediately following this announcement, there appears in the **Federal Register** a copy of revised NIH Guidelines for Research Involving Recombinant DNA Molecules. These revised Guidelines differ from the previous version of the Guidelines promulgated on January 29, 1980 (45 FR 6724) by incorporating within them: changes in the Guidelines which were recommended at the RAC meeting of March 6–7, 1980, and promulgated on April 14, 1980 (45 FR 25366); changes in the Guidelines which were recommended at the RAC meeting of June 5–6, 1980, and promulgated on July 29, 1980 (45 FR 50524); and changes in the Guidelines which were recommended at the RAC meeting of September 25–26, 1980 and which are discussed in this announcement.

I. Proposal To Introduce Genes Cloned in E. Coli K–12 into Arabidopsis Plants Through the Use of Agrobacterium Tumefaciens Carrying an E. Coli/Ti Hybrid Plasmid Vector

In a letter dated March 21, 1980, Dr. Donald J. Merlo of the University of Missouri-Columbia, requested an evaluation of the containment appropriate for the following protocol:

A. A hybrid vector, constructed from the *E. coli* plasmid pBR325 and the origin of replication and transfer genes of *Agrobacterium tumefaciens* plasmid Ti, will be cloned in *E. coli* K–12.

B. *Arabidopsis* DNA will be introduced into the *E. coli*/Ti hybrid plasmid and clone in *E. coli* K–12.

C. The thiamine gene of *E. coli* will bed introduced into the *E. coli*/Ti vector carrying *Arabidopsis* DNA and cloned in *E. coli* K–12.

D. The hybrid plasmid into which *Arabidopsis* DNA and the thiamine gene have been ligated will be transformed into *Agrobacterium tumefaciens.*

E. *Agrobacterium tumefaciens* will be used to introduce the *E. coli*/Ti plasmid vector carrying the *E. coli* Thiamine gene and *Arabidopsis* DNA into *Arabidopsis* plants.

The RAC discussed Dr. Merlo's proposed protocol at the June 5–6, 1980 meeting. The RAC stated that the first three steps of the proposed experiment are covered by Section III–O of the Guidelines. It was agreed that steps D and E are covered by Appendix E and that P3 containment is indicated. However, as the proposed inserted sequences were well characterized, and as *Arabidopsis* DNA will be returned to *Arabidopsis,* the RAC suggested that containment for steps D and E could be lowered to P2.

Since this had not been published in the **Federal Register** for comment prior to the June 5–6, 1980, RAC meeting, this proposed lowering would, however, have to be published in the **Federal Register** for thirty days of comment and re-considered at the September 25–26, 1980 meeting.

In a letter dated July 22, 1980, Dr. Merlo described the proposed experiments in greater detail and requested that the containment conditions for steps D and E be lowered at least to P2 and preferably to Pl.

Dr. Merlo's proposal was published in the August 21, 1980, **Federal Register** (45 FR 55924). No comments were received during the thirty day comment period. The RAC, at its September 25–26, 1980 meeting, once again discussed this issue. A motion to approve the experiments at the P2 level of containment failed by a vote of 4 in favor, 9 opposed, with 3 abstentions. Then, by a vote of 12 in favor, 2 opposed, with 3 abstentions, the RAC recommended approval of the proposed experiments under Pl containment.

I accept this recommendation, and text has been added to Appendix E of the Guidelines indicating this.

II. Request for Certification of a Bacillus Stearothermophilus Derived Plasmid as the Vector Component of an HV1 Bacillus Subtilis Host-Vector System

Dr. David B. Wilson of Cornell University, in a letter dated May 12, 1980, requested certification of a *Bacillus stearothermophilus* derived plasmid, pAB124, as the vector component of an HV1 *Bacillus subtilis* host-vector system. The HV1-certified *Bacillus subtilis* strain RUB331 would be used as the host component.

The RAC discussed this proposal at the June 5–6, 1980 meeting. It was noted that *Bacillus stearothermophilus* is a non-pathogenic thermophile found in soil near hot springs, on compost, etc. In addition, plasmid pAB124 can be transformed into and maintained in *Bacillus subtilis* by natural physiological methods; pAB124 might, therefore, be considered a plasmid indigenous to *Bacillus subtilis.* The committee agreed that this proposal should be published in the **Federal Register** for comment and acted upon at the September 25–26, 1980 meeting.

Dr. Wilson's proposal was published for thirty days of comment in the August 21, 1980, **Federal Register** (45 FR 55925). No comments were received during this period. The RAC once again discussed the proposal at the September 25–26, 1980 meeting. The RAC recommended approval of the proposal by a vote of 18 in favor, none opposed.

I accept this recommendation, and text has been added to Appendix D of the Guidelines indicating this.

III. Request for Certification of a Bacillus Subtilis Strain as the Host Component of an HV2 Host-Vector System

On March 28, 1980, Dr. William Burke, Jr., of Arizona State University, requested certification of *Bacillus subtilis* strain ASB298 as the host component of an HV2 host-vector system. Dr. Burke's request appeared in the **Federal Register** of April 30, 1980 (45 FR 28907). No comments were received during this period. Additional information was submitted by Dr. Burke in a letter dated May 13, 1980.

Dr. Burke's proposal was evaluated by an *ad hoc* working group and subsequently presented to the RAC at the June 5–6, 1980 meeting. One RAC

reviewer said the working group was satisfied with the data presented, and said the single issue not addressed by Dr. Burke concerned the possibility of transfer of genetic information from ASB298 to other *Bacilli* by transformation. After some discussion of this point, the RAC deferred consideration of the proposal pending the submission of additional information on transformation frequencies in soil.

In an addendum dated September 8, 1980, Dr. Burke supplied information on the persistence of ASB298 in sterile soil, and on the frequency of genetic exchange in both soil and under optimized laboratory conditions between strain ASB298 and highly transformable *B. subtilis* strains.

A second notice concerning Dr. Burke's request subsequently appeared in the **Federal Register** of August 21, 1980 (45 FR 55925). No comments on this request were received by the NIH.

The RAC reconsidered this request at its September 25–26, 1980 meeting. On the basis of the strain's characteristics and the frequency of transformation in soil, the RAC recommended, by a vote of 14 in favor, none opposed, and 2 abstentions, that strain ASB298 be certified as the host component of a *B. subtilis* HV2 host-vector system. The RAC specified that ASB898 be used with plasmids certified as the vector components of HV1 *Bacillus subtilis* host-vector systems.

I accept this recommendation, and text has been added to Appendix D of the Guidelines indicating this.

IV. Proposed Amendments Of Section IV–E–2.

In a letter dated April 10, 1980, Dr. Irving Johnson of Eli Lilly and Company, submitted several proposals to amend the Guidelines. One of these proposals would have amended Section IV–E–2 to include the following language:

"Appropriate representatives of industry shall also be chosen to provide expertise in fermentation technology, engineering, and other aspects of large-scale production."

This proposal appeared in the **Federal Register** of April 30, 1980 (45 FR 28908). Two comments were received during the thirty day comment period. One commentator stated that:

"Any attempt to add industrial expertise to the committee * * * is to convert the committee to a self-appointed consensus standards organization."

Another commentator said, "We strongly object to (this) proposal * * *"

The RAC considered this proposal at the June 5–6, 1980 meeting. The committee agreed that, while it would be desirable to have a member with expertise in fermentation technology appointed to RAC, language specifying "representatives of industry" was inappropriate. The RAC agreed that the following amended language should be published for comment and considered at the September 1980 meeting:

"Members should be chosen to provide expertise in fermentation technology, engineering, and other aspects of large-scale production."

In a letter dated July 25, 1980, Dr. Johnson requested that his original language amending Section IV–E–2 be reconsidered at the September 1980 meeting. Dr. Johnson's proposed language and the language constructed by the RAC both appeared for public comment in the **Federal Register** of August 21, 1980 (45 FR 55928). One comment was received during the thirty day comment period:

"We have long held the view that the RAC membership should include persons versed in scientific aspects of industrial microbiology. As with the rest of the Committee, they should be selected for the excellence of their qualifications. Such persons would complement the present technical expertise of RAC by providing knowledge in areas of fermentation technology and large-scale industrial applications. This expertise differs from that of safety engineers and is concerned with basic biological problems of large-scale technology * * *"

The proposals to amend the language of Section IV–E–2 were discussed by the RAC at the September 25–26, 1980 meeting. At that time, the RAC again felt that appointing fermentation technology expertise to RAC was desirable, but that the proposal language specifying appointment of "representatives of industry" was inappropriate. By a vote of 13 in favor, 2 opposed, and 2 absentions, the RAC recommended approval of the following language:

"Members should be chosen to provide expertise in fermentation technology, engineering, and other aspects of large-scale production."

I accept the intent of the RAC recommendation that RAC "members should be chosen to provide expertise in fermentation technology, engineering, and other aspects of large-scale production." I do not believe that it is necessary to change the NIH Guidelines or the RAC Charter in order to assure that the intent of the RAC be honored. This can be accomplished through appointment of one or more individuals with appropriate expertise to fill vacancies that periodically occur in RAC membership.

V. Request to Clone Schizosaccharomyces Pombe DNA in Schizosaccharomyces Pombe Using Hybrid Plasmid Vectors

Dr. Benjamin Hall of the University of Washington requested permission to clone *Schizosaccharomyces pombe* DNA in *Schizosaccharomyces pombe* using approved HV1 *Saccharomyces cerevisiae/E. coli* hybrid plasmids as vectors. Dr. Hall pointed out that *Schizosaccharomyces pombe* has been the subject of intense genetic studies in the laboratory and has been used to ferment beverages for human consumption. He requested that P1 be established as the level of physical containment.

This proposal appeared in the August 21, 1980, **Federal Register** (45 FR 55929). No comments were received during the thirty day comment period.

The RAC discussed this proposal at its September 25–26, 1980 meeting, and recommended approval by a vote of 17 in favor, none opposed.

I accept this recommendation, and text has been added to Appendix E of the Guidelines indicating this.

VI. Proposed Amendment of Appendix E of the Guidelines

In a letter dated July 28, 1980, Dr. Fritz Reusser of The Upjohn Company requested that two sections of Appendix E be amended. These sections currently read as follows:

- "*Bacillus subtilis* strains that do not carry an asporogenic mutation can be used as hosts specifically for the cloning of DNA derived from *E. coli* K–12 and *Streptomyces coelicolor* using NIH-approved *Staphylococcus aureus* plasmids as vectors under P2 conditions.
- "*Streptomyces coelicolor* can be used as a host for the cloning of DNA derived from *subtilis, E. coli* K–12, or from *S. aureus* vectors that have been approved for use in *B. subtilis* under P2 conditions, using as a vector any plasmid indigenous to *Streptomyces coelicolor* or able to replicate in that host by natural biological mechanisms."

The proposed revision would permit additional *Streptomyces* species to be utilized in these experiments. The species to be added are already included in Appendix A, Sublists C and D, as two groups of *Streptomycetes* known to exchange DNA by physiological means. Dr. Reusser noted that these species are not pathogenic for humans, animals or plants. The proposed revised sections of Appendix E would read as follows:

- "*Bacillus subtilis* strains that do not carry an asporogenic mutation can be used as hosts specifically for the cloning

of DNA derived from *E. coli* K–12 and *Streptomyces coelicolor, S. aureofaciens, S. rimosus, S. griseus, S. cyaneus,* and *S. venezuelae* using NIH-approved *Staphylococcus aureus* plasmids as vectors under P2 conditions.

• "*Streptomyces coelicolor, S. aureofaciens, S. rimosus, S. griseus, S. cyaneus,* and *S. venezuelae* can be used as hosts for the cloning of DNA derived from *B. subtilis, E. coli* K–12, or from *S. aureus* vectors that have been approved for use in *B. subtilis,* under P2 conditions, using as vectors any plasmids indigenous to these *Streptomyces* species or able to replicate in these hosts by natural biological mechanisms."

The proposed appeared in the **Federal Register** of August 21, 1980 (45 FR 55928). No comments were received concerning the proposal during the thirty day comment period. The RAC evaluated the proposal at the September 25–26, 1980 meeting, considering and voting separately on each of the two sections proposed to be amended.

With regard to the first section, by a vote of 14 in favor, none opposed, and 3 abstentions, the RAC recommended that the proposed amended language be adopted, i.e.:

• "*Bacillus subtilis* strains that do not carry an asporogenic mutation can be used as hosts specifically for the cloning of DNA derived from *E. coli* K–12 and *Streptomyces coelicolor S. aureofaciens, S. rimosus, S. griseus, S. cyaneus, and S. venezuelae* using NIH-approved *Staphylococcus aureus* plasmids as vectors under P2 conditions."

I accept this recommendation, and this section of Appendix E has been so amended.

The RAC then considered the second section proposed to be amended. During the discussion it was suggested that the language be modified to specify the use of "nonconjugative" plasmid vectors. By a vote of 15 in favor, none opposed, and 2 abstentions, the RAC recommended approval of the following modified language:

• "*Streptomyces coelicolor S. aureofaciens, S. rimosus, S. griseus, S. cyaneus, and S. venezuelae* can be used as hosts for the cloning of DNA derived from *B. subtilis, E. coli* K–12, or from *S. aureus* vectors that have been approved for use in *B. subtilis,* under P2 conditions, using as vectors any nonconjugative plasmids indigenous to these *Streptomyces* species or able to replicate in these hosts by natural biological mechanisms."

Subsequent to the RAC meeting, two comments on this amended language were received by the NIH.

One commentator wrote that the proposal:

"* * *would have the effect of reversing a previous decision by the RAC and increasing the level of containment required for experiments that have been permitted under P2 conditions for some time. Thus, the amendment is a 'major action'; it does not seem appropriate that it be made part of the Guidelines in the absence of a 30-day period providing an opportunity for workers in the field and others to offer comments on it.

"It should also be noted that the concept of 'conjugative' versus 'non-conjugative' plasmids has been derived from enteric bacteria and may not apply to a wide variety of other bacterial species. For example, the mechanism for genetic exchange in *Streptomyces* species is not fully understood; it may be a consequence of hyphal fusion that permits transfer of plasmid and chromosomal genes. If this is true, it may never be possible to isolate a 'non-conjugative' plasmid *per se** * *"

"Since all of the *Streptomyces* species that exchange genetic information with *S. coelicolor* are free-living non-pathogenic soil organisms—and since the change in the Guidelines originally proposed under Action 916 involved genes from only non-pathogenic, well-characterized donor bacteria, I urge your approval of the original proposal without the amendment."

The other commentator wrote:

"I would like to see this amended proposal published for public comment and put to a second vote at the next RAC meeting before you approve this action. The amended proposal failed to receive sufficient consideration of the following points. First of all, in no previous actions regarding *Streptomyces* species was any consideration given during the deliberations to establish levels of physical containment as to whether the vectors were capable of mediating exchange of genetic information. Therefore, this action by the RAC is more restrictive than previous actions and, in my opinion, is inconsistent with the intent of the RAC. In fact, experiments can be carried out at P2 levels of containment in which *B. subtilis, E. coli* K–12, or *S. aureus* vector DNA is cloned into *S. coelicolor* hosts using vectors capable of self-mediated exchange in accordance with Appendix E of the current NIH Guidelines.

"Second of all, the use of the term 'non-conjugative' is inappropriate because the actinomycetes do not exchange genetic information by the process of conjugation as it is known for eubacteria. Rather actinomycetes exchange genetic information by heterokaryosis. In some experiments, the frequency of genetic exchange can be altered by the presence of plasmids and some plasmids can mediate their own transfer to new hosts.

"I feel that to restrict cloning in the actinomycetes to using 'non-conjugative' or non-self-transmissible vectors would be unduly harsh and would severely restrict research with this valuable group of organisms. Considering the level of potential hazard (which I consider minimal) and the potential benefit (which I view as considerable), P2 containment is more than sufficient protection regardless of the vectors employed."

Taking into consideration these comments, I am deleting the requirement for use of nonconjugative plasmids in these systems. If anyone wishes to propose a requirement for use of nonconjugative plasmids in these systems, it will be published for comment in the **Federal Register** as a proposed major action for consideration at a future RAC meeting.

Accordingly, the relevant section of Appendix E has been amended to read as follows:

• "*Streptomyces coelicolor, S. aureofaciens, S. rimosus, S. griseus, S. cyaneus,* and *S. venezuelae* can be used as hosts for the cloning of DNA derived from *B. subtilis, E. coli* K–12, or from *S. aureus* vectors that have been approved for use in *B. subtilis,* under P2 conditions, using as vectors any plasmids indigenous to these *Streptomyces* species or able to replicate in these hosts by natural biological mechanisms."

VII. Request for Consideration of a Proposal to Clone the Tox A Gene of Staphylococcus Aureus

In a memorandum dated July 29, 1980, Drs. Alan G. Barbour and Leonard W. Mayer of the Laboratory of Molecular Structure and Functions, Rocky Mountain Laboratory, National Institute of Allergy and Infectious Dieases, requested an assessment of the containment levels appropriate for cloning the *Staphylococcus aureus* pyrogenic exotoxin type A (Tox A). Drs. Barbour and Mayer indicated that they would prefer to clone the Tox A gene in an HV2 *Bacillus subtilis* host-vector system (since one of the activities of Tox A is enhancement of the toxicity of *E. coli* endotoxin) but, if no HV2 *B. subtilis* host-vector system were available, they requested permission to clone the Tox A gene in an EK2 *E. coli* K–12 host-vector system.

The RAC took this request under consideration at the September 25–26, 1980 meeting. The major determination for the RAC to make was whether Tox A is a "potent toxin" under Section I–D–2 of the Guidelines. It was noted that the lethality of Tox A for animals is not great. The RAC by a vote of 17 in favor, none opposed, recommended that the cloning of the Tox A gene be permitted under P3 containment with either an HV2 *B. subtilis* or an EK2 *E. coli* K–12 host-vector system.

The scientists who submitted this request, noting that one of the activities of Tox A is enhancement of the toxicity of *E. coli* endotoxin, said they preferred to work in *B. subtilis* rather than *E. coli*

if an HV2 *B. subtilis* host-vector system were available. Since an HV2 *B. subtilis* system is in fact now certified (see item III of this announcement) I am approving the cloning of the *Staphylococcus aureus* Tox A gene in an HV2 *Bacillus subtilis* host-vector system at P3 containment. Text has been added to Appendix E indicating this.

VIII. Request for Permission to Transform Chlamydomonas Reinhardi With E. Coli/Saccraromyces Cerevisiae Plasmids.

The RAC at its September 25–26, 1980 meeting considered similar requests from Dr. John Carbon of the University of California, Santa Barbara, and Dr. Stephen Howell of the University of California, San Diego, to introduce *E. coli-Saccharomyces cerevisiae* hybrid plasmids containing defined DNA segments into *Chlamydomonas reinhardi* under P2 conditions. The host is a eukaryotic, unicellular photosynthetic green algae. *C. reinhardi* is non-pathogenic, produces no known toxin, and is not known to exchange genetic information with other organisms.

This proposal was published for comment in the **Federal Register** of August 21, 1980. No comments were received during the thirty day period for comment.

A motion to approve these experiments at the P2 level of containment was passed by a vote of 16 in favor, none opposed, and one absention.

I accept this recommendation, and text has been added to Appendix E of the Guidelines indicating this.

IX. Request For Permission To Transform Candida Albicans With E. Coli-S. Cerevisiae Plasmid.

The following notice appeared in the **Federal Register** of August 21, 1980:

Request for permission to transform Candida albicans with E. coli-S. cerevisiae plasimids. Dr. P. T. Magee of Michigan State University, and Dr. W. LaJean Chaffin of Texas Tech University, have requested consideration of the appropriate containment level for the return of *Candida albicans* DNA to the host of origin. The *Candida albicans* DNA will be cloned in *E. coli* K–12 or in *Saccharomyces cerevisiae* employing a hybrid plasmid vector derived from *E. coli* K–12–S. *cerevisiae* or the yeast 2 micron plasmid.

During the thirty day comment period, no responses were received.

The RAC discussed this proposal at its September 25–26, 1980 meeting. It was noted that *Candida albicans* is a normal inhabitant of the flora of man. It can be a pathogen in compromised individuals but does not produce a toxin. This is basically a return of DNA to host of origin type of experiment, with the intermediate host being either *E. coli* K–12 or *Saccharomyces cerevisiae.*

The RAC by a vote of 14 in favor, 1 opposed, and 3 absentions recommeded approval of this proposal at the P2 level of containment.

I accept this recommendation, and text has been added to Appendix E of the Guidelines indicating this.

X. Proposal To Transform Haemophilus Influenzae With E. Coli/H. Influenzae Hybrid Plasmid

The RAC at its September 25–26, 1980 meeting considered a proposal from Dr. Hamilton Smith of the John Hopkins University to insert an *E. coli* Tn10 tet^R gene into a naturally-occurring *Haemophilus* plasmid and to use the hybrid plasmid to transform *H. influenzae* Rd, a nonpathogenic strain. It was noted that a tetracycline resistance gene found naturally in *Haemophilus* is genetically related to the Tn10 tet^R gene of *E. coli.* A motion to approve these experiments at the P1 level of containment was passed by a vote of 12 in favor, none opposed, with 7 abstentions.

I accept this recommendation, and text has been added to Appendix E of the Guidelines indicating this.

XI. Proposed Exemption For Streptococcus Sanguis And Streptococcus Pneumoniae

A request submitted by Dr. Walter Guild of Duke University Medical Center that *Streptococcus sanguis* and *Streptococcus pneumoniae* be considered as natural exchangers of DNA under the exemption category of Section I–E–4 and Appendix A of the Guidelines was considered by the RAC. This proposal was published for comment in the **Federal Register** of August 21, 1980. No comments were received during the 30 day period for comment prior to the September 25–26, 1980 meeting.

The evidence presented by the investigator demonstrated that these organisms exhange genetic material in both directions by the natural process of transformation. The RAC recommended by a vote of 16 in favor, none opposed, and 1 absention that a new sublist be added to Appendix A of the Guidelines exempting recombinant DNA experiments between *Streptococcus sanguis* and *Streptococcus pneumoniae.*

I accept this recommendation and these two organisms have been added as sublist F of Appendix A.

XII. Request For Permission To Incorporate Recombinant DNA In Zymomonas Mobilis

The RAC considered a request from Drs. B. Montenecourt and D. Eveleigh of Rutgers University to permit the cloning of DNA derived from *Pseudomonas* strains that are non-pathogenic to animals or plants in an *E. coli* K–12 host, followed by transfer of the recombinant DNA into *Zymomonas mobilis.*

This proposal was published for comment in the **Federal Register** of August 21, 1980. No comments were received during the 30 day comment period.

The RAC by a vote of 17 in favor, none opposed and with no abstentions recommended approval at the P2 level of containment for the proposed experiments.

I accept this recommendation, and text has been added to Appendix E of the Guidelines indicating this.

XIII. Request To Transform Protoplasts of Streptosporangium With Recombinant DNA

The RAC at its September 26, 1980 meeting considered a proposal to transform protoplasts of *Streptosporangium* with a hybrid plasmid containing pBR322 plus a *Streptosporangium* plasmid into which have been incorporated specified DNA segments from *Streptomyces* species or an HV1 approved *Bacillus subtilis* cloning vector.

It was noted that members of the *Streptosporangium* genera are soil bacteria and have never been implicated in any human, animal, or plant diseases. Further, these nutritionally fastidious organisms have not been reported to produce toxins harmful to humans.

The motion to approve these experiments at the P2 level of containment was passed by a vote of 17 in favor, none opposed, and 1 abstention.

I accept this recommendation, and text has been added to Appendix E of the Guidelines indicating this.

XIV. Proposed Revision of Subsections of Section III–C–1–e

A notice appeared in the **Federal Register** of January 31, 1980 concerning proposed revision of Section III–C–1–e, and its subsections. It was recommended that Section III–C–1–e, III–C–1–e–(1), III–C–1–e–(1)–(a), and III–C–1–e–(1)–(b), of the Guidelines be changed and that a new Section III–C–1–e–(1)–(c) be added. Section III–C–1–e–(2) would remain unchanged. The RAC, at its March 6–7, 1980 meeting, recommended adoption of Section III–C–

1–e, III–C–1–e–(1), and III–C–1–e–(1)–(a) as published in the **Federal Register** of January 31, 1980, with certain modifications in Section III–C–1–e–(1)–(a).

The Director, NIH, accepted this recommendation and promulgated the following sections in the **Federal Register** of April 14, 1980:

"III–C–1–e. All Viral Vectors.

"III–C–1–e–(1). Other experiments involving eukaryotic virus vectors can be done as follows:

"III–C–1–e–(1)–(a). Recombinant DNA molecules containing no more than two-thirds of the genome of any eukaryotic virus [all viruses form a single Family (36) being considered identical (50)] may be propagated and maintained in cells in tissue culture using P1 containment. For such experiments, it must be shown that the cells lack helper virus for the specific Families of defective viruses being used. The DNA may contain fragments of the genomes of viruses from more than one Family but each fragment must be less than two-thirds of the genome."

At its March 6–7, 1980 meeting, the RAC voted to defer consideration until the June 5–6, 1980 meeting of the new Sections III–C–1–e–(1)–(b) and III–C–1–e–(1)–(c) as proposed in the **Federal Register** of January 31, 1980, and requested that a working group develop additional information. Accordingly, a working group met on May 13, 1980, during the annual meeting of the American Society for Microbiology in Miami Beach, Florida. The report of the working group was considered briefly at the June 5–6, 1980 RAC meeting when it was decided that it would be considered again by the RAC at its September 25–26, 1980 meeting.

The Working Group discussed the question of the appropriate containment conditions for experiments involving recombinant DNA molecules containing less than two-thirds of the genome of any eukaryotic virus which may be rescued with helper virus. On the basis of the consensus of the virologists, the following recommendation was proposed, as a revision of Section III–C–1–e–(1)–(b) of the Guidelines:

"III–C–1–e–(1)–(b). Recombinants with less than two-thirds of the genome of any eukaryotic virus may be rescued with helper virus using P2 containment if wild type strains of the virus are CDC Class 1 or 2 agents, or using P3 containment if wild type strains of the virus are CDC Class 3 agents (1)."

This proposal was published for comment in the **Federal Register** of August 21, 1980. During the thirty day comment period no responses were received.

At the September 25–26, 1980 meeting, the RAC discussed this proposal again. Some members of the committee expressed concern whether the rescue of a defective recombinant virus with helper virus could result in the formation of a virus with an altered host specificity or increased pathogenicity. It was noted that the working group of virologists previously discussed this point, and reached the conclusion that the recombinant virus would pose no greater biohazard than the wild type virus used as a helper. The consensus of the working group was that the level of containment required for rescue of the recombinant virus should correspond to the same level of biohazard as the helper virus as determined by the CDC classification.

The motion to accept the proposed revision of subsection III–C–1–e–(1)–(b) was passed by a vote of 10 in favor, 5 opposed, and 1 abstention.

I accept this recommendation, and Section III–C–1–e–(1)–(b) has been so modified. This modification justifies two further changes in the Guidelines. First, new text has been added to Section III–C–1 to advise the reader of the relationship of the subsections of Sections III–C–1–a, III–C–1–b, III–C–1–c, and III–C–1–d of the Guidelines to the subsections of Section III–C–1–e. Also, Table IV of the Guidelines has been eliminated.

XV. Proposed Containment For Cloning Between Members of the Actinomycetes Group

Dr. Dean Taylor of the Smith Kline and French Laboratories, proposed that the third entry in Appendix E of the Guidelines be modified to read:

P2 physical containment shall be used for DNA recombinants produced between members of the *Actinomycetes* group except for those species which are known to be pathogenic for man, animals, or plants.

This proposal was made previously by the RAC Working Group on Prokaryotic Host-Vectors Other Than *E. coli* and appeared in the **Federal Register**, April 13, 1979 (44 FR 22316). The RAC considered the proposal at its May 21–23, 1979 meeting and recommended to restrict this so that it did not include the entire *Actinomycetes* group but rather only the genera *Streptomyces* and *Micromonospora*. The Director, NIH, accepted this recommendation and the action was published in the **Federal Register**, July 20, 1979 (44 FR 42916), and appears as the third entry in Appendix E of the Guidelines.

This proposal was published for comment in the **Federal Register** of August 21, 1980. During the 30 day comment period, no comments were received.

During the RAC discussion of this proposal it was noted that the family of *Actinomycetes* include many genera that are not pathogenic for man, animals, or plants. The microorganisms in this group are mainly found in soil, and are of medical and industrial importance. They produce ninety percent of the antibiotics used in medicine. Although some members of the group are parasitic, most do not cause disease, or are marginal pathogens.

A motion to restrict the proposal to members of the *Actinomycetes* group which are known not to be pathogenic for man, animals, or plants, failed by a vote of 3 in favor, 11 opposed, with 3 abstentions.

A motion to accept the proposal as published in the **Federal Register** on August 21, 1980, passed by a vote of 16 in favor, 1 opposed, with 1 abstention.

I accept this recommendation, and the third entry in Appendix E of the Guidelines has been so amended.

XVI. Changes in Registration Requirements

Dr. Maxine Singer, National Cancer institute, National Institutes of Health, proposed a series of changes in the administrative requirements specified by the Guidelines. The proposal would elimnate NIH review, registration, and approval for all experiments assigned containment conditions in the Guidelines.

In submitting the proposal, Dr. Singer stated:

When the Guidelines were first promulgated, many arguments appeared to dictate a complex system of review and approval prior to the initiation of experiments. Regardless of how one views the wisdom of the earlier decisions, the multi-level system with its emphasis on central review at the NIH is now clearly unnecessary, inhibitory, expensive, and conterproductive in relation to the respect accorded the containment recommendations. By now, Institutional Biosafety Committees have accumulated sufficient expeience with and knowledge of the Guidelines to operate as independent review groups. Safety Officers now function in many research institutions. Furthermore, the good laboratory practices mandated by the Guidelines have become routine practice in many laboratories. Indeed, confidence in the efficiacy of Guidelines has been based primarily on compliance by individual investiators within their own laboratories. The administrative changes that accompanied the revised containment levels for experiments with *E. coli* K–12 and *S. cerevisiae* earlier this year recognized that central review and approval were no longer necessaryily desirable or useful. The present proposal is an extension of that idea.

In brief, the proposal eliminates central review, registration, and approval for all

experiments assigned containment conditions in the Guidelines. Investigators would be required to notify their Institutional Biosafety Committees prior to the initiation of experiments and those committees would be responsible for reviewing the registration documents for consistency with the provisions of the Guidelines and advising the investigators of necessary changes. No Memoranda of Understanding would be required. IBCs and investigators would still be expected to petition the ORDA regarding experiments not explicitly covered by the Guidelines, experiments requiring case-by-case review and experiments involving exceptions to the provisions (or prohibitions). The NIH and the RAC would function as policy making elements with responsibility to change the Guidelines as required, to evaluate containment requirements for experiments not explicitly covered by the Guidelines, and for consideration of exceptions.

Seven years have passed since the scientific community first raised questions regarding recombinant DNA experiments. The ignorance of those early years has been supplanted with a wealth of experience and information. Just as the early stringent Guidelines were promptly adopted in response to the ignorance, we must now respond just as promptly to the current more realistic appraisals.

The proposed revisions were published in the **Federal Register** of August 21, 1980, for comment, as Item 8 of the notice. Specific changes were proposed in many different places in the Guidelines, specified under subheadings "A" through "X" within Item 8.

Seventeen letters were received commenting on the proposal. Sixteen commentators supported its adoption. One commentator stated:

Maxine Singer's initiative (**Federal Register**, August 21, 1980) to have the NIH Guidelines fall primarily under local control is both wise and timely. Decisions about scientific research are best left to the investigtors both for efficiency and as a matter of fundamental principle. Only in exigency, should this ideal be violated. Perhaps we've passed through such an occasion with R–DNA research. However, it is now the time to return to the more normal situation. Since work with recombinant DNA has proven to be very safe and very important, dual review at the national and local levels serves no good purpose.

As one involved from the beginning in the R–DNA issue, I've always felt that the 'Guidelines' should be guidelines; they turned into regulations. With the proposed change, they will revert and also the unfortunate quasi-regulatory role that the NIH has had to play will begin to disappear.

Another commentator said:

I think the IBC mechanism has proven its effectiveness in interpreting and enforcing the letter and intent of the Guidelines governing recombinant DNA research. I do not see how the practices of submission, obtaining and recording, etc., of MUA's particularly the requirements for annual submissions of MUA's for each continuing NIH grant or for applications for new grants, contributes to the safety of research. An updated statement of work in progress from each investigator to the IBC's would be significantly simpler to administer and would ensure as much real safety as the present system.

Another observed:

I agree with her that the function of review, registration, and monitoring of research workers falling into categories explicitly mentioned in the Guidelines can be effectively administered by the local Institutional Biosafety Committees. This would reduce the workload for ORDA allowing it to spend more time determining policy and revising the Guidelines according to requests or to new data. It would simultaneously ease the bureaucratic workload for the researcher without jeopardizing the effectiveness of the Guidelines. Not only are the procedures described in the Guidelines now standard practice among most laboratories, as pointed out by Dr. Singer, but I feel that the local Institutional Biosafety Committees are in much better position to evaluate compliance with the Guidelines. Because of their past experience with the Guidelines, I feel that these committees are ideally suited to take over this important administrative role.

One commentator made the following observation about Institutional Biosafety Committees:

Institutional Biosafety Committees clearly seem able to operate as independent review groups, and the laboratory practices set forth in the Guidelines have now become part of the standard operating procedures of laboratories working in the field. In other fields of biological research, safety procedures are implemented entirely at the local level, even when known biohazards are involved. It is no longer necessary to have a unique multi-level system in an area where seven years of extensive experience has shown the absence of a unique hazard.

Another commentator said the following about central review:

Elimination of central review at NIH for experiments classified in the Guidelines will save a great deal of time for both the investigator and the reviewers at NIH. I believe the experience of the past six years justifies a change toward an administrative arrangement long successfully practiced in the handling of proven microbial pathogens, namely national guidelines enforced by local biosafety committees.

One commentator made the following observation about the current system of NIH review:

The present complex system of review on both local and Federal levels is no longer necessary. It is wasteful of time, effort, and money. It is, in fact, counterproductive because bureaucratic requirements seen by investigators to be clearly unnecessary lead to disrespect for regulations that should be respected. Institutional Biosafety Committees should, in my opinion, be fully capable of monitoring laboratory practices and containment levels specified by the Guidelines.

Another letter included the following remark:

I strongly endorse the proposed changes because I believe that the risks of this research are now clearly minimal and because the bureaucracy and consequent wasted time are truly detrimental to progress in an area that promises to be of great benefit to mankind.

The Chairman of one IBC reporting the unanimous endorsement of his committee stated:

We feel strongly that safety is solely a function of the effectiveness of the local institutional practices, on the part of the PI's and the IBC, in complying with and enforcing the Guidelines. The submission of MUAs adds nothing but expensive and time-consuming paperwork.

The one letter against the proposal stated the following:

At present, we do not believe that there are good reasons for changing the registration requirements. Although present procedures demand some extra paperwork, they permit centralized keeping of files which could be of significant use in reviewing the extent of work on recombinant DNA and its possible hazards. Somebody should know what is going on.

The RAC discussed the proposal at length at its September 25–26, 1980 meeting. Dr. Singer, who attended this portion of the meeting, summarized the proposal and presented her arguments for adopting it. It was noted that the proposal has two major aspects, which could be acted upon separately. The first aspect is that it would eliminate NIH review of protocols for which containment levels are specified by the Guidelines. The second aspect is that the proposal would eliminate the requirement for pre-review by the local IBC prior to initiation of all experiments for which containment levels are specified by the Guidelines (Prior review is already not required for most experiments). Some members of the RAC felt that adoption of the proposal should be delayed until a broad-based survey of the functioning of IBCs is completed. Some members of the RAC felt that pre-review of all experiments by the IBC should not be eliminated at the present time. The RAC then voted separately on a four-part motion proposed by Dr. Gottesman.

The RAC voted 15 in favor, 3 opposed, with no abstentions, to eliminate the requirement for NIH review of IBC decisions on any experiments for which containment levels are specified in the Guidelines.

The RAC voted 12 in favor, 5 opposed, with 1 abstention, to defer consideration

of eliminating pre-review of experiments by the IBCs until the frequency of principal investigator error in selecting the appropriate containment levels has been determined.

The RAC voted 17 in favor, none opposed, with 1 abstention, that IBCs keep records of recombinant DNA research done in their institution, including a record of the frequency of errors in classificaion of experiments by the principal investigator.

The RAC voted 15 in favor, 3 opposed, with no abstentions, that IBCs no longer need register with NIH recombinant DNA experiments for which containment levels are specified in the Guidelines.

I accept these recommendations.

The four-part motion passed by the RAC indicated the intent of the RAC to recomment acceptance of certain concepts in the proposal by Maxine Singer (i.e., elimination of the requirement for iBC registration with, and NIH review of, experiments for which the containment levels are specified in the Guidelines), but to defer recommendation of other concepts (i.e., the proposal to eliminate pre-review by the IBC for these experiments).

As noted earlier, the proposal by Maxine Singer published as Item 8 in the **Federal Register** of August 21, 1980, consisted of proposed changes in many different places of the Guidelines, specified under subheadings "A" to "X". Following the RAC meeting, I asked a four-person group to revise these proposed changes in order to translate the four-part general motion of the RAC into specific Guideline changes. The group (consisting of Dr. Bernard Talbot, my Special Assistant, Dr. William Gartland, Director of the Office of Recombinant DNA Activities, Dr. Maxine Singer, originator of the proposal, and Dr. Susan Gottesman, RAC member and originator of the four-part motion passed by the RAC) unanimously agreed on wording which translates the intent of the RAC into specific changes in the Guidelines. I have accepted their recommendations.

The result is that some of the changes "A" through "X" originally proposed by Dr. Singer have been accepted as proposed; some have been rejected, thereby leaving the relevant portions of the Guidelines unchanged; and some have been further modified so that particular sections now are different from both the Guidelines prior to the Singer proposal and from the Singer proposal.

Specifically, the sections where the changes proposed by Dr. Singer have been accepted are: "E"—Deletion of Section IV–C–3; "F"—Deletion of Sections IV–D–1–C and IV–D–1–C–(1) through IV–D–1–C(5); "G"—Deletion of Section IV–D–1–d; "H"—Amendment of Section IV–D–2–f; "I"—Amendment of Section IV–D–2–h; "K"—Amendment of Section IV–D–3–b; "L"—Amendment of Section IV–D–3–f; "P"—Amendment of Section IV–D–5–c–(3); "U"—Deletion of Section IV–E–3–b, IV–E–3–c–(1), IV–E–3–c–(2), and IV–E–3–c–(3); "V"—Deletion of Section IV–E–4–a; and "W"—Deletion of Sections IV–F–1 and IV–F–2.

The proposed changes which have been rejected thus leaving the Guidelines as they were previous to the Singer proposal are: "Q"—Heading of Section IV–D–5–d; "R"—Heading of Section IV–D–5–e; and "T"—Proposed deletion of Section IV–E–1–b–(3)–(e).

The proposed changes which have been further modified so that the sections now read differently from the Guidelines prior to the Singer proposal and from the Singer proposal are: "A"—Section III; "B"—Section III–0; "C"—Last sentence of Section III–A–3–a; "D"—Last sentence of Section III–A–3–b; "J"—Section IV–D–3–a; "M"—Section IV–D–5–a–(1); "N"—Section IV–D–5–b–(4); and "O"—Section IV–E–5–b–(5).

In addition, Sections IV–F–3, IV–F–4, and VI–C, dealing with registration, have been eliminated, as has the proposed Section IV–D–5–e–(6).

One consequence of these changes is that MUAs need no longer be filed with NIH and the term "MUA" has been deleted from the Guidelines.

One part of the RAC four-part motion called for IBCs to keep records of recombinant DNA research done in their institution, including a record of the frequency of errors in classification of experiments by the principal investigator. This requirement for record keeping will be specified in the revision of the Administrative Practice Supplement to the NIH Guidelines to be issued in November 1980.

During the RAC discussion, the concept of requiring the IBCs to report annually to NIH on all recombinant DNA research being done at the institution was rejected. NIH is sponsoring a meeting of IBC Chairmen on November 24–25, 1980. The issue of possibly reporting annually to NIH will be discussed at that meeting. Following that discussion, I will again review this issue.

It should be emphasized that NIH remains responsible for specifying containment conditions for all experiments not explicitly covered by the Guidelines. This includes experiments requiring case-by-case review and exceptions to the provisions or prohibitions of the Guidelines. Principal investigators must petition NIH for consideration of such proposed experiments. NIH will follow existing procedures in such cases and will notify the principal investigators as before. No such experiments are to be approved by the IBCs until containment conditions have been set by the NIH. No such experiments are to be initiated by PIs until appropriate registration documents have been submitted to and approved by the IBC. The registration documents should include the NIH statement of containment conditions.

XVII. Procedures For Review of Large-Scale Experiments

Section I–D–6 of the Guidelines prohibits "large-scale experiments (e.g., more than 10 liters of culture) with organisms containing recombinant DNA's, unless the recombinant DNAs are rigorously characterized and the absence of harmful sequences established."

Section IV–E–1–b–(3)–(d) of the Guidelines states that the Director, NIH, is responsible for "authorizing under procedures specified by the RAC, large-scale experiments (i.e., more than 10 liters of culture) for recombinant DNAs that are rigorously characterized and free of harmful sequences."

Part VI of the Guidelines, "Voluntary Compliance," encourages institutions not otherwise covered by the Guidelines to follow the standards and procedures set forth in the Guidelines.

At its September 1979 meeting, the RAC adopted the following procedures to be followed by applicants proposing to exceed the 10-liter limit:

"Application Procedures for Large-Scale Recombinant DNA Experiments

"1. For each research project proposing to exceed the 10-liter limit, the applicant shall file a request with the NIH Office of Recombinant DNA Activities (ORDA). The request should include the following information:

"a. The Memorandum of Understanding and Agreement (MUA) submitted to the local Institutional Biosafety Committee. The MUA should include, or have appended to it, a summary paragraph which describes the proposed project in language that is comprehensible to non-specialists.

"b. A statement of the rationale for wishing to exceed the 10-liter limit.

"c. A specification of the total volume of the fermenter to be used.

"d. Evidence that the recombinant DNAs to be employed in the research have been rigorously characterized and are free of harmful sequences.

"e. A description of the applicant's laboratory practices, containment equipment, and facilities relevant to the containment of large volumes of culture.

"f. Evidence of the applicant's or applicant institution's previous experience in handling large volumes of culture. Applicants should exhibit knowledge of state-of-the-art procedures for working with large volumes of microorganisms.

"g. A description of procedures to be employed for the inactivation and disposal of large volumes of culture.

"h. A description of procedures for containing and inactivating accidental spills, should they occur.

"2. Each request submitted to ORDA shall be referred to a working group of the NIH Recombinant DNA Advisory Committee for review.

"3. Following review and approval by the working group, each request shall be submitted to the entire Recombinant DNA Advisory Committee for review.

"4. Following review and approval by the RAC, each request shall be submitted to the Director, NIH, for final review.

"5. Applications for large-scale experiments which are submitted by institutions not receiving NIH funds for recombinant DNA research shall be kept confidential (provided the institutions so desire) in accordance with the provisions of the NIH Guidelines for Research Involving Recombinant DNA Molecules.

"These procedures may be refined or revised on the basis of discussion and action by the NIH Recombinant DNA Advisory Committee."

At recent RAC meetings, there have been extensive discussions of the role of the RAC and NIH in the review of large-scale proposals submitted by industry. (Minutes of RAC meetings are available from ORDA.) At the June 1980 meeting, the RAC passed a motion by a vote of seventeen to zero with one abstention that the following proposal be published in the **Federal Register** for consideration at the September 1980 meeting:

"The following procedures should be adopted for approval of requests to grow greater than 10 liters of organisms containing recombinant DNA. The RAC will determine if a given recombinant DNA-containing strain is rigorously characterized and the absence of harmful sequences established. Such a determination shall include specification of the containment level (P–LS). These determinations should not in any way be construed as RAC certification of safe laboratory procedures for industry scale-up. Adherence to the specified containment conditions is the responsibility of the local IBC."

This proposal was published for comment in the **Federal Register** of August 21, 1980. There it was pointed out that if the proposal were accepted, it would have the effect of changing the application procedures to read as follows:

"Application Procedures for Large-Scale Recombinant DNA Experiments

"1. For each research project proposing to exceed the 10-liter limit, the applicant shall file a request with the NIH Office of Recombinant DNA Activities (ORDA). The request should include the following information:

"a. The Memorandum of Understanding and Agreement (MUA) submitted to the local Institutional Biosafety Committee. The MUA should include, or have appended to it, a summary paragraph which describes the proposed project in language that is comprehensible to non-specialists.

"b. A statement of the rationale for wishing to exceed the 10-liter limit.

"c. Evidence that the recombinant DNAs to be employed in the research have been rigorously characterized and are free of harmful sequences.

"d. Specification of the P–LS level proposed to be used as defined in the NIH *Physical Containment Recommendations for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules.* (**Federal Register**, April 11, 1980).

"2. Each request submitted to ORDA shall be referred to a working group of the NIH Recombinant DNA Advisory Committee for review.

"3. Following review and approval by the working group, each request shall be submitted to the entire Recombinant DNA Advisory Committee for review.

"4. Following review and approval by the RAC, each request shall be submitted to the Director, NIH, for final review.

"5. Applications for large-scale experiments which are submitted by institutions not receiving NIH funds for recombinant DNA research shall be kept confidential (provided the institutions so desire) in accordance with the provisions of the NIH Guidelines for Research Involving Recombinant DNA Molecules.

"These procedures may be refined or revised on the basis of discussion and action by the NIH Recombinant DNA Advisory Committee."

During the comment period, two comments were received.

One commentator stated:

> I regret that the RAC wishes to terminate its reviews of engineering plans for proposed private-sector DNA operations.

Another letter stated:

> We agree with the RAC proposal passed in June 1980, to exclude regulatory functions dealing with industrial scale-up. We believe that the current mission of the RAC is appropriate and that its present constitution, representing scientific and public interests, is not well suited for a regulatory role. Other bodies of the federal government already have the mandate to carry out regulatory functions and should acquire necessary resources and expertise.

The proposal was discussed at length at the September 25–26, 1980 RAC meeting.

Dr. Krimsky said that although at previous RAC meetings he had argued strongly for proposals like this, he had now changed his mind, because he had come to realize that such pre-review as the RAC has been performing is unique, and that no other agency would conduct such a review. He proposed, as an alternative proposal, that there be established a subcommittee of the RAC made up of some members of the RAC and some members of NIH staff with expertise in facilities and technologies, and that the subcommittee request representation from the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), the Center for Disease Control (CDC), and the Environmental Protection Agency (EPA). In this proposal, the subcommittee would review engineering and technology, and its review would be transmitted directly to the Director, NIH. After discussion, this alternative motion was withdrawn from consideration for the time being, with the understanding that it would be reconsidered later in the meeting.

During further discussion of the proposal as published in the **Federal Register** of August 21, 1980, Dr. Fedoroff indicated her support for eliminating RAC review of the details of physical containment for individual large-scle proposals, as is already the case for small-scale research. Dr. King indicated her support of the proposal as an acceptable compromise.

Following further discussion, the RAC voted 12 in favor, 5 opposed, with one abstention, to adopt the proposal as published in the **Federal Register** of August 21, 1980. I accept this recommendation and procedures for its implementation are published at the end of this section.

Later in the meeting, Dr. Krimsky introduced the following motion to establish a large-scale review subcommittee:

"An industrial review subcommittee of the RAC shall be established with the responsibility for advising the Director on procedures and facilities design pertaining to applications for large-scale operations.

"After the full RAC has reviewed the biological containment requirements for

a large-scale proposal, the subcommittee shall examine the applicant's plans for large-scale operations and issue recommendations to the Director on plant design, health surveillance and environmental monitoring. The Director shall advise institutions of recommended design parameters and operational procedures. The determination shall not be construed as NIH certification of industrial operations.

"The subcommittee shall invite participation from NIH's biosafety staff plus OSHA, NIOSH, CDC, FDA, EPA, and USDA."

Dr. Fedoroff expressed concern about delays if first the full RAC and then subsequently a subcommittee were to be involved in the review process. Others agreed. Dr. Gottesman said that she was opposed to continuation of review of equipment design in individual applications by either the full RAC or subcommittee. Dr. Logan of OSHA, speaking in behalf of the proposal, said that the delays need not be serious and that such subcommittee review would be beneficial. He said that OSHA does not have the legal authority to conduct pre-review of applications. Dr. Campbell said that while he opposed a subcommittee doing pre-review of individual applications, he favored a subcommittee to prepare future revisions of the Physical Containment Recommendations for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules (i.e., the definitions of Pl-LS, etc.) and to monitor how well the system is working. Dr. Gottesman proposed an amendment to Dr. Krimsky's motion to establish the subcommittee with these functions, but to do no pre-review of individual applications. An amendment to this amendment proposed by Dr. Krimsky to include subcommittee pre-review of individual applications failed by a vote of 3 in favor, 15 opposed, with no abstentions. After further amendments were adopted, the RAC passed the following motion by a vote of 15 in favor, 2 opposed, with 1 abstention:

"A large-scale review subcommittee of the RAC shall be established with the responsibility for advising the RAC on procedures and facilities design pertaining to large-scale operations, and on the performance of local IBCs in reviewing physical containment facilities.

"The subcommittee shall invite participation from NIH's biosafety staff plus OSHA, NIOSH, CDC, FDA, EPA, and USDA."

I agree with the establishment of a group to report to the RAC on recommendations for future revisions of the Physical Containment Recommendations for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules (i.e., the definitions of P1-LS, etc.) and on the performance of local IBCs in reviewing large-scale physical containment facilities. A Working Group of the RAC was established at the May 1979 meeting to develop the Physical Containment Recommendations for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules. These recommendations were reviewed at the December 1979 and March 1980 RAC Meetings before being published in the **Federal Register** on April 11, 1980. Establishing a new "subcommittee" of the RAC to deal with this issue would require a formal change in the RAC Charter. Therefore, I favor reconstitution of the current RAC "Working Group" for this purpose. As noted above (see item IV of this announcement), the RAC has recommended that RAC "members should be chosen to provide expertise in fermentation technology, engineering, and other aspects of large-scale production." I expect that an individual with these qualifications will shortly be appointed. When this happens, I will ask that the appointee consult with the RAC Chairman and that together they decide on which additional RAC members should be appointed to the reconstituted Large-Scale Review Working Group. The RAC recommended that participation be invited from "NIH's biosafety staff plus OSHA, NIOSH, CDC, FDA, EPA, and USDA." Ideally, all Federal agencies with representatives on the RAC should be invited to participate in the deliberations of the Working Group.

In accordance with the recommendation of the RAC, the Working Group will not be involved in pre-review of individual applications. To assist in its function of advising the RAC on the performance of local IBCs in reviewing physical containment facilities and on future revisions of the Large-Scale Physical Containment Recommendations, the Working Group may request information from individual companies. Since NIH is not a regulatory agency, the intent of any such information collection will be fact-finding, to help in development of general recommendations from the Working Group to the RAC, and not for purposes of regulatory actions directed at individual companies.

In response to recommendations of the RAC, the revised application procedures for large-scale proposals are now promulgated as final, i.e.:

"Application Procedures for Large-Scale Recombinant DNA Experiments.

"1. For each research project proposing to exceed the 10-liter limit, the applicant shall file a request with the NIH Office of Recombinant DNA Activities (ORDA). The request should include the following information:

"a. The registration document submitted to the local Institutional Biosafety Committee. This should include, or have appended to it, a summary paragraph which describes the proposed project in language that is comprehensible to non-specialists.

"b. A statement of the rationale for wishing to exceed the 10–liter limit.

"c. Evidence that the recombinant DNAs to be employed in the research have been rigorously characterized and are free of harmful sequences.

"d. Specification of the P–LS level proposed to be used as defined in the NIH *Physical Containment Recommendations for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules. (Federal Register,* April 11, 1980).

"2. Each request submitted to ORDA shall be referred to a working group of the NIH Recombinant DNA Advisory Committee for review.

"3. Following review and approval by the working group, each request shall be submitted to the entire Recombinant DNA Advisory Committee for review.

"4. Following review and approval by the RAC, each request shall be submitted to the Director, NIH, for final review.

"5. Applications for large-scale experiments which are submitted by institutions not receiving NIH funds for recombinant DNA research shall be kept confidential (provided the institutions so desire) in accordance with the provisions of the NIH Guidelines for Research Involving Recombinant DNA Molecules and to the extent permitted by law.

"These procedures may be refined or revised on the basis of discussion and action by the NIH Recombinant DNA Advisory Committee."

These application procedures are identical to those published for comment on August 21, 1980, except for the elimination of the term "Memorandum of Understanding and Agreement," its replacement by the term "registration document," and addition of the clause "and to the extent permitted by law" in paragraph 5. As discussed above (in item XVI of this announcement), the term "Memorandum of Understanding and Agreement" has been eliminated from the Guidelines. The revised Guidelines, in Section III, describe the

required contents of a registration document.

The revised "Application Procedures for Large-Scale Recombinant DNA Experiments" differ from the previous version (adopted at the September 1979 RAC meeting) in requiring that the application specify a "P–LS" level at which the work will be done, rather than requiring individual details of physcial containment. In other respects the Application Procedures adopted at the September 1979 RAC meeting remain identical in the revised Application Procedures promulgated today. As noted in the minutes of the September 6–7, 1979 RAC meeting, review of each large-scale proposal by the RAC, "might be at a meeting, but it also might be through mail ballot." This option will be retained.

Additional Announcements of the Director, NIH

Section IV-E-1-b-(3)-(d) of the Guidelines gives responsibility to the Director, NIH, for "authorizing, under procedures specified by the RAC, large-scale experiments (i.e., involving more than 10 liters of culture) for recombinant DNAs that are rigorously characterized and free of harmful sequences."

Accordingly, several requests for authorization to culture, on a large-scale, recombinant DNA host-vector systems have been received and reviewed by the NIH.

I. Genentech, Inc.

On November 4, 1980, the Director, NIH, on the recommendation of the RAC, approved a request from Genentech, Inc., for the large-scale culture up to 750 liters of EK1 host-vector systems containing plasmids into which have been ligated cDNA coding for human leukocyte interferons.

This request was approved with the understanding that Genentech, Inc., has agreed to permit an observer, designated by NIH, to visit the facilities if NIH should choose to inspect the site.

The principal investigators are Drs. Michael Ross and Norm S. C. Lin. The work is to be done at the P1–LS level of containment at the research and development facility at 460 Point San Bruno Boulevard, South San Francisco, California 94080.

II. Burns-Biotec Laboratories, Inc.

On November 4, 1980, the Director, NIH, approved requests from Burns-Biotec Laboratories, Inc., a wholly-owned subsidiary of Schering Corporation, for large-scale culture of EK1 host-vector systems containing plasmids coding for human leukocyte interferon, and certain derivatives thereof, in a 1000 liter fermentor (up to 750 liter working volume) at the P1–LS level of containment.

The request was approved with the understanding that Burns-Biotec Laboratories, Inc., has agreed to permit an observer, designated by NIH, to visit the facilities if NIH should choose to inspect the site. The principal investigator for this project is Dr. Donald E. Baldwin. The large-scale growth of the organisms is to be carried out at plant facilities located in Elkhorn, Nebraska.

Dated: November 14, 1980.

Donald S. Fredrickson,

Director, National Institutes of Health.

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592) requires a statement concerning the official government programs contained in the *Catalog of Federal Domestic Assistance.* Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because of the guidance in this notice covers not only virtually every NIH program but also essentially every federal research program in which DNA recombinant molecule techniques could be used, it has been determined to be not cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every federal program would be included as many federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the *Catalog of Federal Domestic Assistance* are affected.

NIH programs are not covered by OMB Circular A–95 because they fit the description of "programs not considered appropriate" in Section 8–(b)–(4) and (5) of that Circular.

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